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| 09/466,935 | 12/20/1999 | VITALIY ARKADYEVICH LIVSHITS | 0010-1070-0 | 1750 |

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| EXAMINER | |
|---|---|
| STEADMAN, DAVID J | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1652 | 25 |

DATE MAILED: 08/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Advisory Action | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/466,935 | LIVSHITS ET AL. | |
| | Examiner | Art Unit | |
| | David J Steadman | 1652 | |

*--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

THE REPLY FILED 23 July 2003 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____.

3. ☐ Applicant's reply has overcome the following rejection(s): _____.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *see attachment*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: *16 and 17*.

   Claim(s) objected to: _____.

   Claim(s) rejected: *37-48*.

   Claim(s) withdrawn from consideration: *49-63*.

8. ☐ The proposed drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)( PTO-1449) Paper No(s). _____.

10. ☐ Other: _____

**ADVISORY ACTION**

**[1]** Claims 16, 17, and 37-63 are pending in the application.

**[2]** Claims 16 and 17 appear to be in a condition for allowance.

**[3]** Claims 37-48 stand finally rejected.

**[4]** Claims 49-63 are withdrawn from consideration as being drawn to a non-elected invention.

**[5]** Applicant's cancellation of claims 18-36 and addition of claims 37-63 in Paper No. 24, filed July 23, 2003, is acknowledged.

**[6]** The request for reconsideration is acknowledged, however the amendment does not place the application in condition for allowance for the reasons stated below.

**[7]** The written description rejection of claims 37-48 under 35 USC 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in previous Office actions (see item 5 of Paper No. 21, item 7 of Paper No. 18, and item 3 of Paper No. 10, and item 15 of Paper No. 7). Applicant argues (beginning at the bottom of page 10 of Paper No. 24) the amended claims specify the following for increasing the activity of RhtC: expression of the DNA, increasing a copy number of the DNA, or substitution of a promoter. Applicant presents references (D1 (WO 92/10561), D2 (EP 0127328 A2), D3 (US 5,595,889), D4 (abstract of JP 03-147791), D5 (abstract of JP 03-147792), and D6 (WO 98/04715) in asserting increasing DNA copy number and promoter substitution are well known methods for increasing protein activity. Applicant argues reference D6 demonstrates substitution of an endogenous promoter with an exogenous promoter results in increased expression of the threonine operon and teaches the following examples of exogenous promoters: lac, trp, $P_L$, $P_R$, lpp, and tac promoters. Applicant argues that based on the teachings of reference D6, applicant is in possession of the present invention. Applicant's argument is not found persuasive. There is no dispute that increased DNA expression by transformation of a bacterium with an expression vector comprising said DNA or promoter substitution of an endogenous bacterial promoter with a lac, trp, $P_L$, $P_R$, lpp, or tac promoter as taught by references D1-D6 are all well-known methods for increasing the level and therefore activity of a given protein. However, this does not relieve applicant from adequately describing

the claimed genus of isolated modified bacteria. For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a *representative number of species* by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406. MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In this case, the specification discloses only two representative species of the claimed genus of modified bacteria, i.e., an *Escherichia* bacterium transformed with an expression vector comprising a nucleic acid encoding SEQ ID NO:4 and optionally transformed with an expression vector comprising a nucleic acid encoding SEQ ID NO:2. The specification fails to describe any additional representative species of the claimed genus. While MPEP § 2163 acknowledges that in certain situations "one species adequately supports a genus", it is also acknowledges that "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus". In the instant case, the claimed genus of *Escherichia* bacteria encompasses species that are widely variant having *any* modification that results in increased DNA expression of a protein that makes the bacteria L-threonine resistant and optionally wherein increased DNA expression is a result of increased DNA copy number (by *any* modification) or promoter substitution (by *any* promoter). As such, the disclosure of the single representative species of an *Escherichia* bacterium transformed with an expression vector comprising a nucleic acid encoding SEQ ID NO:4 and optionally transformed with an expression vector comprising a nucleic acid encoding SEQ ID NO:2 is insufficient to be representative of the attributes and features of *all* species encompassed by the claimed genus of bacteria. Given the lack of description of a representative number of polynucleotides, the specification fails to sufficiently describe

the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention. While applicant's cited references demonstrate that bacterial transformation with an expression vector comprising a desired protein encoding DNA or promoter substitution of an endogenous promoter with a lac, trp, $P_L$, $P_R$, lpp, or tac promoter are well known techniques known for increasing protein expression, these references fail to demonstrate possession of the claimed genus of bacteria. For example, as noted by applicant, reference D6 teaches substitution of an endogenous promoter with the following exogenous promoter: lac, trp, $P_L$, $P_R$, lpp, or tac promoter. The structures of the promoter of the threonine operon and lac, trp, $P_L$, $P_R$, lpp, and tac promoters are well known in the art. However, it is noted that the claims are not so limited to a modified bacterium having substitution of the endogenous RhtC promoter with any of the exemplified promoters of reference D6. Instead, the instant claims encompass bacteria having a promoter substituted with *any* other promoter having any nucleotide sequence – including promoters that have not been disclosed in the specification and have yet to be isolated. As applicant has described only two representative species of a genus that encompasses widely variant species, applicant was clearly not in possession of the claimed invention at the time of filing of the instant application.

**[8]** The scope of enablement rejection of claims 37-48 under 35 USC 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in previous Office actions (see item 6 of Paper No. 21, item 8 of Paper No. 18, and item 4 of Paper No. 10, and item 16 of Paper No. 7). Applicant argues the instant specification provides a detailed description for preparing and using the claimed bacterium and refers to pages 8-36 of the specification. Applicant argues references D1-D6 (as cited above) demonstrate that increasing DNA copy number and promoter substitution are well known means for increasing protein activity. Applicant argues that in view of the detailed teachings of the specification and the knowledge of the art as evidenced by references D1-D6, one can make the entire scope of claimed bacteria by routine experimentation. Applicant's argument is not found persuasive. The examiner maintains that the scope of claimed bacteria are not enabled by the specification and the prior art according to the detailed analysis of the Factors of *In re Wands* as set forth

at pages 6-8 of Paper No. 21 and undue experimentation would be required for a skilled artisan to make the entire scope of claimed bacteria. As stated above, there is no dispute that increased DNA expression by transformation of a bacterium with an expression vector comprising said DNA or promoter substitution of an endogenous bacterial promoter with a lac, trp, $P_L$, $P_R$, lpp, or tac promoter as taught by references D1-D6 are all well-known methods for increasing the level and therefore activity of a given protein. However, neither the specification nor the specification in combination with the prior provides guidance that would enable the broad scope of claimed modified bacteria. As noted above in regard to reference D6, the structures of the promoter of the threonine operon and lac, trp, $P_L$, $P_R$, lpp, and tac promoters are all well known in the art such that one of skill can substitute the promoter of the threonine operon with a lac, trp, $P_L$, $P_R$, lpp, or tac promoter by homologous recombination. However, the modification of the claimed *Escherichia* bacteria is not limited to substitution of the RhtC promoter with a lac, trp, $P_L$, $P_R$, lpp, or tac promoter. Instead, the claims are so broad as to encompass *all Escherichia* bacteria having *any* modification that results in increased DNA expression of a protein that makes the bacteria L-threonine resistant and optionally wherein increased DNA expression is a result of increased DNA copy number (by *any* modification) or promoter substitution (by *any* promoter). Based on the detailed analysis of the Factors of *In re Wands* as set forth at page 6-8 of Paper No. 21, the specification in combination with the prior art fail to enable the broad scope of claimed bacteria. Thus, in view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, and the high degree of unpredictability as described in a detailed analysis of the Factors of *In re Wands* as set forth at page 6-8 of Paper No. 21 and for the reasons stated above, undue experimentation is necessary for a skilled artisan to make and use the entire scope of the claimed invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The Examiner can normally be reached Monday-Friday from 7:00 am to 5:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX number for submission of official papers to Group 1600 is (703) 308-4242. Draft or informal FAX communications should be directed to (703) 746-5078. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman
Patent Examiner
Art Unit 1652

REBECCA E. PROUTY
PRIMARY EXAMINER
~~GROUP 1800~~
1600